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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PD/4-32804A	FOR FURTHER ACTION See Form PCT/IPEA/416	
International application No. PCT/EP2004/003513	International filing date *(day/month/year)* 02.04.2004	Priority date *(day/month/year)* 04.04.2003
International Patent Classification (IPC) or national classification and IPC A61K31/435, A61K31/436, A61K47/02, A61K47/10, A61K47/14, A61K47/44		
Applicant NOVARTIS AG et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 1 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.10.2004	14.11.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Kling, I Telephone No. +49 89 2399-8471

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/003513

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-13 as originally filed

   Claims, Numbers

   1-5 received on 19.10.2004 with letter of 04.10.2004

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/003513

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 3

because:

☒ the said international application, or the said claims Nos. 3 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/003513

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-5
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-5
Industrial applicability (IA)	Yes:	Claims	1,2,4,5
	No:	Claims	3

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 3 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

For the assessment of the present claim 3 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

1 The following documents are referred to in this communication:

D1: WO 96/13249 A (SANDOZ AG ; SCHMOOK FRITZ (AT); POPP XUE PING (CH); JACKMAN MARTIN (CH) 9 May 1996 (1996-05-09)

D2: WO 00/32234 A (NOVARTIS ERFIND VERWALT GMBH ; NOVARTIS AG (CH); KRIWET KATRIN (DE); R) 8 June 2000 (2000-06-08)

D3: KAPP A ET AL: "LONG-TERM MANAGEMENT OF ATOPIC DERMATITIS IN INFANTS WITH TOPICAL PIMECROLIMUS, A NONSTEROID ANTI-INFLAMMATORY DRUG" JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, MOSBY - YEARLY BOOK, INC, US, vol. 110, no. 2, August 2002 (2002-08), pages 277-284, XP009032310 ISSN: 0091-6749

D4: WO 97/25977 A (CIBA GEIGY AG ; TIEMESSEN HARRY (DE)) 24 July 1997

(1997-07-24)

D5: EP-A-0 812 588 (YOSHITOMI PHARMACEUTICAL) 17 December 1997 (1997-12-17)

D6: EP-A-1 273 288 (NOVARTIS ERFIND VERWALT GMBH ; NOVARTIS AG (CH)) 8 January 2003 (2003-01-08)

D7: GB-A-2 327 610 (NOVARTIS AG) 3 February 1999 (1999-02-03)

D8: EP-A-1 064 942 (FUJISAWA PHARMACEUTICAL CO) 3 January 2001 (2001-01-03)

D9: US 2002/044967 A1 (IBUKI RINTA ET AL) 18 April 2002 (2002-04-18)

D10: WO 2004/016289 A (NOVARTIS PHARMA GMBH ; NOVARTIS AG (CH); SEKKAT NABILA (CH); KRIWET KA) 26 February 2004 (2004-02-26)

D11: WO 03/074054 A (NOVARTIS PHARMA GMBH ; NOVARTIS AG (CH); BABIOLE SAUNIER MAGGY (FR); B) 12 September 2003 (2003-09-12)

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 to 5 is not new in the sense of Article 33(2) PCT.

WO-A-9613249 provides a topical composition, in the form of an emulsion, that comprises a compound of the FK506 class: 33-epi-chloro-33-desoxy-ascomycin; and glycerol; an unsaturated fatty alcohol and water and also a topical pharmaceutical composition that comprises a macrolide in suspension. In a further aspect, this invention provides the use of an unsaturated fatty alcohol to stabilise the 33-epi-chloro-33-desoxy-ascomycin in a pharmaceutical composition.

The topical compositions defined above are useful in the treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically mediated diseases. Examples of such diseases are psoriasis, atopic dermatitis, contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis, Lichen planus. Pemphigus, bullous Pemphigoid, Epidermolysis bullosa, urticaria. angioedemas, vasculitides, erythemas. cutaneous eosinophilias. Lupus erythematous and Alopecia areata. See in particular the examples 23, 24, 25 and 26 and also claims 1 to 8 and page 5, first paragraph.

This teaching anticipates the subject-matter of claims 1 to 5.

WO-A-0032234 relates to topical compositions comprising ascomycins, such as 33-epi-chloro-33-desoxy-ascomycin (see page 2) and a carrier vehicle such as cetyidimethicone copolyol, polyglyceryl-4-isostearate or glycerol (see the description page 11).
This teaching anticipates the subject-matter of claims 1 to 5.

WO-A-9725977 relates to a process for preparing an emulsion composition comprising 33-epi-chloro-33-desoxy-ascomycin or a derivative thereof as active agent and a stabiliser selected from a phospholipid, a glycolipid, a sphingolipid, a diacylphosphatidyl glycerol, an egg-phosphatidylglycerol, a soy-phosphatidyglycerol, a diacyl-phosphatidylglycerol, or a salt thereof; or a saturated, mono- or di-unsaturated (C12-24) fatty acid, or a salt thereof, and c) an organic solvent. The composition is used for injection and in the treatment of atopic dermatitis, contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis.
This teaching anticipates the subject-matter of claims 1 to 5.

EP-A-1 273288 discloses an emulsion composition comprising 33-epi-chloro-33-desoxy-ascomycin or derivative thereof and an emollient selected from a phospholipid, a glycolipid, a sphingolipid, a diacylphosphatidyl glycerol, an egg-phosphatidylglycerol, a soy-phosphatidylglycerol, a diacyl-phosphatidylglycerol, or a salt thereof.
This teaching anticipates the subject-matter of claims 1 to 5.

D7 discloses a pharmaceutical composition for topical application comprising a macrolide, preferably 33-epi-chloro-33-desoxy-ascomycin which is stabilised by the presence of glycerol monostearate. The composition is used for the treatment of plaque psoriasis.
This teaching anticipates the subject-matter of claims 1 to 5.

D8 relates to sustained release of macrolide compounds preferably 33-epi-chloro-33-desoxy-ascomycin. Macrolide compounds are used for preventing bone marrow transplant rejection or organ transplant rejection and for treating and preventing autoimmune disorders, inflammatory disorders (such as eczema, atopic dermatitis and

myocarditis). These compositions are administered orally.

US2002044967 provides an oral formulation of a macrolide compound where the dissolution of the macrolide compound is under sustained release; and a sustained-release formulation containing a composition in solid solution, where the macrolide compound is present at an amorphous state in a solid base adsorbate of fk506, tacrolimus, ascomycin, ethyl rapamycin, desoxyascomycin,etc...

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 to 5 does not involve an inventive step in the sense of Article 33(3) PCT.

Re Item VI

Certain documents cited

The current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the documents P,X cited in the international search report could become relevant to assess whether claims 1 to 5 satisfy the criteria set forth in Article 33(1) PCT.

WO2004016289 published 20040226
relates to single-phase topical liquid or semi-solid pharmaceutical compositions substantially free of ethanol and water and comprising an ascomycin, such as 33-epi-chloro-33-desoxy-ascomycin in a carrier vehicle.

WO03074054 published 20030912
relates to topical ophthalmic compositions comprising an ascomycin such as 33-epi-chloro-33-desoxy-ascomycin e.g. for the treatment of inflammatory diseases such as blepharitis.
Applicants have now found that ophthalmic compositions comprising an ascomycin and a carrier comprising a medium chain fatty acid triglyceride and/or isopropyl myristate are highly efficient and well tolerated by the ocular tissue.

Patent Claims

1. A pharmaceutical composition comprising 33-epichloro-33-desoxyascomycin in combination or association with an emollient selected from the group consisting of dimethicone, glycerol and isostearylstearate together with at least one pharmaceutically acceptable diluent or carrier.

2. A pharmaceutical composition of claim 1 wherein the emollient is present in an amount from about 10% to about 5000% w/w of the amount of 33-epichloro-33-desoxyascomycin.

3. A method of treatment of a dermatological or mucosal disease in a subject suffering from such a disease comprising co-administering synergistically effective amounts of a composition of claim 1.

4. A process for the preparation of a composition of any one of claims 1 or 2 comprising mixing 33-epichloro-33-desoxyascomycin and an emollient selected from the group consisting of dimethicone, glycerol and isostearylstearate in combination or association with at least one pharmaceutically acceptable diluent or carrier.

5. A kit of parts comprising 33-epichloro-33-desoxyascomycin and an emollient selected from the group consisting of dimethicone, glycerol and isostearylstearate in separate unit dosage forms, together with instructions for use.

IL/4-Oct-2004